OpenFlowChem – a platform for quick, robust and flexible automation and self-optimisation of flow chemistry

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Abstract

Flow chemistry is a time-saver in the laboratory and a cost-saver in industry partly because of automation and autonomous operation. Nevertheless, a batch process is often preferred over a flow counterpart because setting up the autonomous operation may take a lot of time. In the paper, we propose a novel open-access OpenFlowChem platform based on Labview for process automation, control and monitoring. The platform is optimized for quick system setup, reconfiguration and high flexibility. The platform is demonstrated in three examples: autonomous operation with an automatic stepwise program, proportional–integral–derivative (PID) control and self-optimization. In the first example, the system automatically executed a reaction program defined in a spreadsheet file to study reversibility of a Pd/SiO_2 catalyst poisoning with quinoline in the reaction of alkyne semihydrogenation. The addition of quinoline increased alkene selectivity and reduced the catalyst activity, but the time required to remove the catalyst poison varied by a factor of 10 and depended on the poison concentration. In the second example, a PID controller adjusted the nitrobenzene concentration in a hydrogenation reaction to compensate for catalyst deactivation and a disturbance in process parameters. The PID controller kept constant the hydrogen consumption determined by an inline optical liquid sensor. In the third example, the product yield in alkyne semihydrogention was self-optimized adjusting the flow rates of the substrate, the catalyst poison (quinoline) and the solvent in a tube reactor coated with a 5 wt% Pd/SiO_2 catalyst. As a result, the alkene yield reached 96.5%.

1. Introduction

Manual operations are ever-present, but performing routine repetitive tasks is worse than improper - it is inefficient. Robots are substituting people for many conveyor-type production activities. In science, many reports show that replacing a person with an automated system not only decreases the operational costs but improves speed, reliability and safety of a process.[1–4] Flow chemistry, similarly, substitutes labour-intensive "artisan" batch manufacture with a conveyor-belt approach.[5] The flow processes improve productivity, safety, product selectivity, open new cost-saving opportunities and reaction shortcuts.[6–9] A combination of the continuous flow process with online analytical equipment opens the possibility for telescoping and autonomous operation to reduce the costs and the process development time.[10–13] Automation is also applicable to batch processes making autonomous or high-throughput systems demonstrated by Symyx or Chemspeed.[3,14,15] Elimination of human-induced variability and tight automatic process control in flow chemistry provides the quality-by-design and receives encouragement from the regulators such as US FDA.[16,17]

Creation of autonomous flow chemistry systems, however, is challenging because the systems contain many components that should be re-configured and re-connected to perform a different process. The hardware of a flow system can be connected and prepared in a matter of hours or days. Implementation of a smooth system control and process monitoring, however, often requires significantly more time. Therefore, a researcher faces a tough choice of either spending efforts on performing a study/synthesis manually or doing labour-intensive automation. Not surprisingly, Ley and co-workers noted that flow chemistry often requires more time at the lab bench compared to batch.[18]

One may argue that a flow chemist should focus on the manipulation and transformation of the substances, rather than automation. However, the freedom to focus on the chemical transformation rather than routine manipulations allows performing complex multistage syntheses unimaginable even several years ago with the automated reactors.[11–13,18,19] The growing literature demonstrates the advantages of autonomous operation and requires knowledge of not only chemistry and engineering but information spheres.[18] Using automation, the chemist can "outsource" a significant fraction of the routine experimental tasks to an automated flow system and focus on the chemistry.[20]

The majority of automation systems are a task-specific and are almost never disseminated, so other researchers have to re-invent them repeatedly. There are only a few researchers who share the automation codes, notably O'Brien and Ingham.[21–25] The lack of automation dissemination is exemplified by only a handful groups in the world which demonstrated the process self-optimisation of chemical reactors.[10,26–29] Poliakoff and co-workers showed self-optimisation in various reactions, optimised for the product yield and even obtained several products from the same system.[19,27,30,31] Jensen and co-workers compared self-optimisation algorithms and showed the possibility for intensified data collection by ramping the experimental conditions.[32–34] The autonomously-operated reactors were demonstrated to be efficient in obtaining full kinetic data for complex reaction networks.[10,32,35–38] The problem is that even a minor alteration of an automation system, in our experience, requires a considerable amount of efforts (measured in days, sometimes in weeks), which decreases the benefits of automation. Recently, Fitzpatrick et al.[26] have suggested an excellent cloud-based LeyLab automation approach. However, we believe that such an advanced system is not always required and the setup time may be excessively high for many flow chemistry operations.

In this paper, we present a novel open-access flow automation platform OpenFlowChem, which is designed for creating flexible control and automation systems, their quick deployment and rapid modifications. The platform is demonstrated in three examples of hydrogenation in flow. Firstly, catalyst poisoning reversibility study in an automated stepwise reaction with pre-defined steps. Secondly, hydrogenation of nitrobenzene operating under constant hydrogen consumption with an inline liquid sensor and the reactor controlled by a proportional–integral–derivative (PID) algorithm. Thirdly, 3-dimensional self-optimisation of an alkynol semihydrogeantion in the presence of catalyst poison with the online gas chromatographic analysis. The technical details are provided in the Supplementary material, the software is freely available on the web.[39]

2. Options and requirements for automating flow chemistry

Summarising the previous works on automation,[26,29,31,34,40,41] we consider that the automation solutions for lab to pilot processes have the following main requirements: (i) operational safety, (ii) robustness – high reliability and stability to instrument and communication errors, (iii) the ability for automated as well as a fully manual control, (iv) quick extendibility, (v) low entry level for the system alteration, (vi) build-in datalogging, (vii) visual interface with (viii) the ability for the remote control and operation. While maintaining high safety standards, these requirements can be clustered into the groups of flexibility (points ii-iv) and costs in the broader sense of financial, time and operational efforts (points v-viii).

Figure 1 shows a schematic relationship between the flexibility and the costs for flow automation systems. The commercial systems are cheap (often free), but narrow in scope because of the focus on a particular unit or a manufacturer. The commercial systems are excellent for simple tasks (such as controlling a single pump) or complex narrowly-defined tasks (controlling an HPLC system with multiple detectors). Therefore, if the experimental work involves integration of multiple units and feedback algorithms, the commercial solutions become insufficient. The bespoke solutions (software created by subcontractors or the flow chemists) are more expensive because of additional time and resources needed to build the system. However, the bespoke nature of the solution provides excellent flexibility and allows for an unlimited range of instruments and tasks performed.

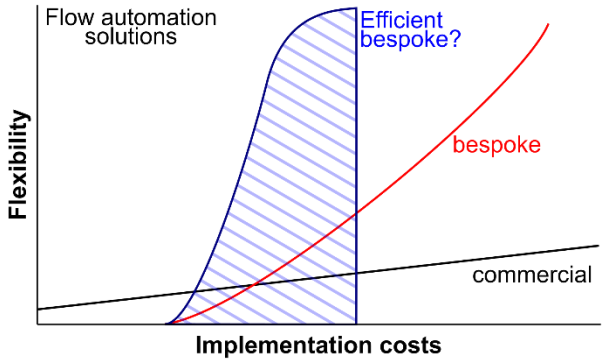

Figure 1 Outline of the existing reactor automation solutions in terms of application flexibility and the implementation costs. The crossed region represents the missing possibility for highly flexible yet simple solution presented in the paper.

The bespoke systems are often designed in an ad-hoc manner and need to be significantly re-designed every time the system or the task changes. In the flow chemistry literature, the majority of the systems

are controlled by Labview which allows visual programming.[11–13,28,32–34,42–44] Often, the systems are controlled by Matlab due to its excellence in implementing complex computational tasks such as optimisation.[29,30,36] To combine the advantages of both systems, researchers place the Matlab code inside the Labview programs.[12,13,32–34,36] Unfortunately, this practice lacks modularity requiring major programming efforts for any alterations.

In such "enclosed" systems, however, when one instrument is removed, the whole program including the Matlab codes have to be carefully modified and re-checked. Similarly, the specialised programming literature usually focuses on developing very narrow automation solutions that lack flexibility. This literature, moreover, often demands the knowledge of the programming conventions[41,43,44] and jargon which results in a very steep learning curve barely justifiable for automation tasks routinely found in flow chemistry.

The OpenFlowChem platform presented in this paper aims at simplicity and speed of the automation solutions, high flexibility at low marginal cost as in the area hatched in Figure 1. The OpenFlowChem platform contains three major layers: (i) device monitors, fully self-sufficient programming units, to handle *all* interactions with individual instruments, (ii) a system module to provide integration and interaction between the individual instruments, (iii) optional external safety devices to ensure an additional system-independent safety margin. The systems may be externally controlled or interact horizontally for additional flexibility and modularity. The implementation details are covered in the Supplementary information (S1, S2).

Connection of many instruments requires making only quick-fix fluidic connections. The same way, the OpenFlowChem architecture provides the ability to assemble complex control systems made of various units by plugging the programming elements responsible for the instruments. Programming of the system integration module requires little to no instrument-specific knowledge, but an understanding of the system operation logic. This way, the most demanding programming tasks of creating the device monitors may be outsourced or dedicated to the programming staff. The flow chemist can create a reliable system in a matter of hours in contrast to days or weeks using the conventional approaches. All the subsequent re-arrangement of the flow equipment will require modifications only in the system module to be completed within hours – often faster than the physical re-arrangement of the hardware.

The OpenFlowChem architecture can be coded using many free and commercial programming products. We believe, however, that Labview provides the lowest implementation costs even despite the price of the software and a rather unusual visual programming concept. The main advantages of Labview include the possibility for (i) quick communication with the majority of laboratory instruments and (ii) efficient expansion and building of the holistic system. The former comes from the existence of the freely available instrument drivers – the components that convert the high-level commands such as "set flow to 1 mL min^{-1}" into a particular expression required for a given instrument. Although simple in principle, the task of sending a basic instrument instruction may take weeks for many advanced systems such as mass-flow controllers. The existence of the instrument drivers provided by the manufacturer even for simple systems often improves reliability and accelerates programming the device monitors. The other reason for using Labview is the possibility to run a large number of instances in a pseudo-parallel mode in exactly the same way as running a single instance. For example, once a device monitor for an HPLC pump is completed, it can be cloned to run 4 HPLC pumps in a matter of 5 minutes (Supplementary Information S3). Lastly, the visual nature of the Labview language is very similar to creating block diagrams of the system operation. Hence, the flow chemist responsible for developing the system logic

can easily implement the system integration module, test its operation and introduce modifications if required.

Strongly believing in open access research, we provide our source codes to allow the community to further develop the approach and use our device monitors for programming of their flow systems. In these systems, we avoided or minimised advanced programming concepts often presented in the specialised literature and neglected some conventions to minimise the introduction barriers.

3. Application examples

In the following examples, we cover three flow chemistry systems exemplified by hydrogenation reactions carried out inside catalyst-coated tube reactors. The reactors were provided by Stoli Catalysts Ltd. The examples are sufficiently diverse to represent a wide variety of the tasks encountered in flow chemistry practice and include an automatic execution of a pre-defined list of tasks, in-line analysis with feedback control and self-optimisation.

3.1. Automatic stepwise operation

The automated stepwise operation involves carrying out a reaction according to a pre-defined program. This operation mode may seem not advanced, however, it is the most suitable for routine screening under identical conditions, proof of principle tests or time on stream experiments.[42,45–47] In this case, the system reads a spreadsheet file with all the reaction conditions (temperature, pressure, flow rates), the duration of each step and the amount of sample to be taken for product analysis by a fraction collector.

In this example, we studied reversibility of the poisoning and used a fraction collector for a quick sampling. The catalyst poison (quinoline) increases the selectivity to the semihydrogenation product, but it is not clear if the poison can be removed from the catalyst on seconds or years.[48–50]. Solutions of 0.5 M 2-methyl-3-butyn-2-ol (MBY, substrate) and 0.5 M quinoline in isopropanol (IPA) were fed with two HPLC pumps (Knauer P4.1S) and mixed with a T-joint (Figure 2a). The total liquid flow rate was maintained constant at 1 mL min^{-1} in this experiment. Hydrogen was added with a system of Bronkhorst mass-flow controllers at the hydrogen to substrate ratio of 1.1. The gas-liquid flow passed through a 1 m catalyst-coated tube reactor containing a 5 wt% Pd/SiO_2 catalyst described elsewhere.[46,51] The reactor was placed in a convection oven. The reaction pressure was controlled with an Equilibar back-pressure regulator controlled by an analogue Proportional Air GX1 controller operating via an ICP-DAS M-7026 digital to analogue converter. The liquid samples were collected in 2 mL vials using a Zang Autosam360 fraction collector. The samples were analysed with an off-line gas chromatograph (Shimadzu GC-2010) equipped with a Stabilwax 10m x 0.15mm x 0.15μm column and a flame ionization detector (FID).

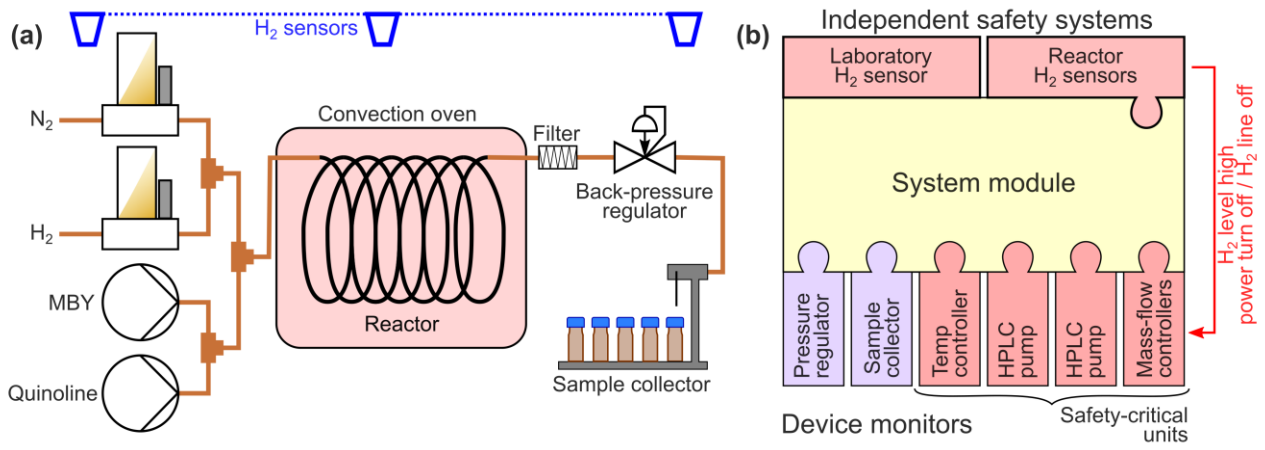

Figure 2. (a) Scheme of the reactor used in the automated stepwise study of the quinoline poisoning reversibility in 2-methyl-3-butyn-2-ol (MBY) semihydrogenation. (b) Scheme of the OpenFlowChem automation system with the jigsaw joints showing digital communication.

Figure 2b shows the structure of the OpenFlowChem system which contains the device monitors of the corresponding instruments. The safety devices include (i) a laboratory hydrogen sensor that shuts down the mains hydrogen flow and (ii) a set of three hydrogen sensors (Figaro TGS821) read by an Arduino microcontroller. The latter is incorporated into the system as a device monitor and can power down the safety-critical instruments: mass-flow controllers, the HPLC pumps and the oven. Setting up of the reactor system took around 10 days for plumbing and wiring, about 15 days for electrical installations, while the reactor automation took only about 20 h, the vast majority of this time was spent preparing the device monitors (now available online[39]).

Figure 3 shows a simplified block diagram of the system module. The device monitors start the instruments, and the system waits till all the instruments are connected. The spreadsheet file with the reaction parameters is read, and the setpoints are sent to the device monitors. The system waits for the time pre-defined in the spreadsheet file to reach the reaction steady state. After the sample is taken by the fraction collector, the next row from the spreadsheet file is executed. The file is read after every step which allows for modifications of the next steps during the experiment. While sampling or waiting, the system is continuously monitoring for the system-level (across several instruments) alarms such as a substantial increase in the pressure drop. The instrument-specific alarm conditions (such as the deviation in the flow rates or overpressure) are checked by the device monitors. The system module stops all the device monitors if any critical alarm is received.

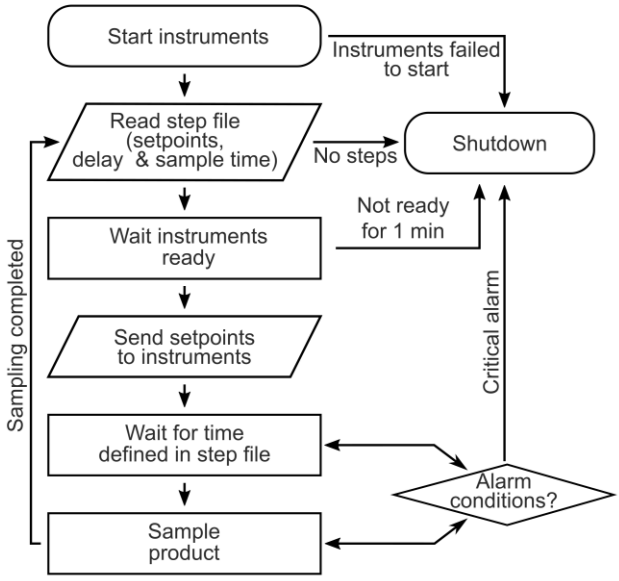

Figure 3. Block diagram of the OpenFlowChem system module of the automatic stepwise hydrogenation reactor that executes parameters pre-defined in the step file.

Figure 4a shows the scheme of the MBY hydrogenation reaction, where alkenol (2-methyl-3-buten-2-ol, MBE) is the target product, and over-hydrogenation to alkanol (2-methyl-2-butanol, MBA) is the side-reaction. The MBY conversion (X_{MBY}) was calculated with Equation 1, where C_X are concentrations of the corresponding species. The selectivity (S_{MBE}) was calculated with Equation 2. These equations assume 100% carbon balance, which was above 99% for all the conditions studied.

$$X_{MBY} = 1 - \frac{C_{MBY}}{C_{MBY}+C_{MBE}+C_{MBA}}, \quad (1)$$

$$S_{MBY} = \frac{C_{MBE}}{C_{MBE}+C_{MBA}}. \quad (2)$$

Figure 4b demonstrates that both the MBY conversion and the MBE selectivity stabilised around the values of 48.0% and 96.6%, respectively, in the absence of quinoline. The selectivity observed is rather high compared to the typical value of around 92% for the Pd/SiO_2 or Pd/TiO_2 catalysts,[49,52–54] and the selectivity increased with the addition of quinoline. The highest selectivity of 97.8% was observed at the highest quinoline concentration which agrees with literature data.[48,49,55] Surprisingly, the MBY conversion increased with the addition of quinoline. This observation seems counter-intuitive considering that quinoline is well known to decrease the catalyst activity.[48,49,55] However, the addition of quinoline decreased the initial MBY concentration because the total liquid flow rate was kept constant. Therefore, a high conversion corresponds to a lower initial MBY concentration. For example, a very similar conversion for the 0.5 M MBY (the first 20 min on stream) and the 0.45 M MBY + 0.05 M quinoline (around 40 min on stream) indicates decreasing catalyst activity by about 10% in the presence of quinoline.

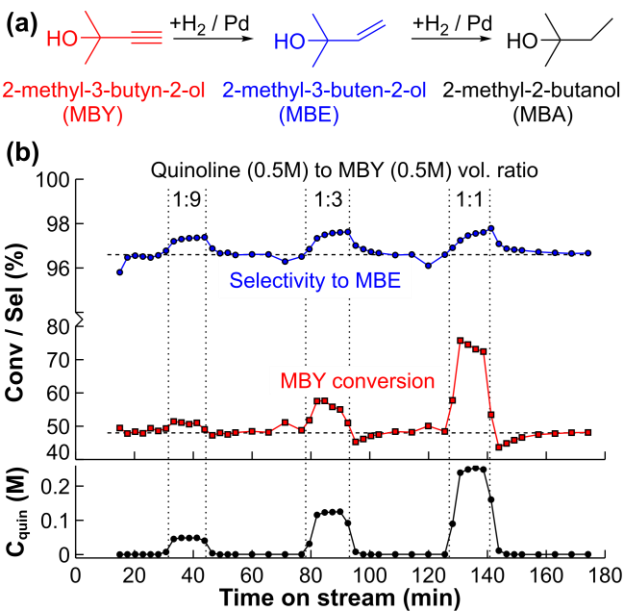

Figure 4. (a) Scheme of the 2-methyl-3-butyn-2-ol (MBY) semihydrogenation reaction. (b) MBY conversion and MBE selectivity inside a 1 m tube reactor wall-coated with a 5 wt% Pd/SiO_2 catalyst in the presence of pulses of quinoline in various MBY/quinoline ratios. Reaction conditions: the total liquid flow rate 1 mL min^{-1}, H_2 flow 30 mL min^{-1} (STP), atmospheric pressure and the reaction temperature of 35 ºC.

Figure 4b demonstrates that the catalyst fully recovers to the initial performance observed prior to the quinoline addition. However, the recovery time depends strongly on the poison concentration and can vary between 2 and 20 minutes in the concentration range studied. This information is important for the catalyst operation, scaling up the processes and a follow-up study performed in example 3.3.

The automated stepwise operation of the flow reactor allowed for a labour-efficient study on the reversibility of the catalyst poisoning. Performing such a study manually would need the experimenter to collect the samples manually spending all the time near the reactor while controlling all the conditions which increases the chances of a mistake.

3.2. Maximising catalyst utilisation with a PID control

In this example, the problem of maximising throughput of a heterogeneously catalysed gas-liquid hydrogenation of nitrobenzene is addressed by adjusting the operating parameters to compensate for the catalyst deactivation and external disturbances. Performing such an operation either manually or in the automatic stepwise fashion as in example 3.1 seems impractical because it requires an extensive parameter optimisation study. Moreover, during the reactor operation, the product samples need to be analysed and the parameters manually adjusted to accommodate the catalyst deactivation – the operation barely feasible in practice.

A widely used industrial approach of providing a substantial performance margin to ensure high conversion even over a significantly deactivated catalyst is not only inefficient (only a fraction of the catalyst activity is utilised) but detrimental for the catalyst and product properties. For example, side reactions such as oligomerisation can occur over a prolonged catalyst contact, and the noble metals may leach into the reaction medium requiring further metal removal steps and reduced catalyst lifetime.[56–58] An elegant way to solve the problem is to adjust the experimental parameters using a closed-loop

feedback algorithm and an inline sensor to ensure maximum reactor throughput even despite the catalyst deactivation.[58]

We used a PID (proportional–integral–derivative) algorithm to adjust the reaction conditions along with the changes in the catalyst behaviour. The PID algorithms are often used in temperature controllers, but seldom in chemical reactors to control the reaction rate. In the case of a temperature PID controller, the algorithm has a setpoint (for example, 80 ºC) and a process variable (current temperature reading) is adjusted using a control parameter (power of a heater).

In the case of a hydrogenation chemical reactor, the obvious process variable is the substrate conversion (chemical composition of the product). There are numerous methods to study the composition such as online or inline liquid or gas chromatographs,[10,19,29–32,34] infrared,[18,26,27,33,36] UV-vis,[42] Raman,[11,36,38] mass-[26,37] and NMR spectrometry.[11,28,35] However, all these methods are very costly, which creates a high adoption barrier for applications.[59] In the case of a gas-liquid reaction, a more affordable approach is to monitor the hydrogen consumption using either a gas flow meter or an inline liquid sensor placed downstream the reactor.

Prior to the reaction study, we compared two methods of measuring the gas consumption – using an optical liquid inline sensor and a thermal mass-flow meter (Supplementary S4). The mass-flow meter was measuring the flow rate of gas in the product stream after the liquid was collected in a trap. The liquid sensor was measuring if liquid or gas is inside the studied point of the tube, which on averaging over time provides the liquid hold up or the fraction of the liquid in the gas-liquid stream.

The mass-flow meter, although calibrated for hydrogen, proved to be unreliable for the analysis of hydrogen consumption because (i) it required a long (~5 min) time to reach steady state readings and (ii) the systematic error introduced by the solvent evaporation into the gas phase. The optical liquid sensor was more reliable with short response time (~5s). Liquid hold up, however, determined by the liquid sensor depended on the tube diameter and liquid properties (density, viscosity and surface tension) because only liquid plugs were measured as liquid leaving unaccounted the liquid film that always surrounds the gas plugs.[60,61]

To perform the PID-controlled hydrogenation, a different reactor was built schematically presented in Figure 5. The system contains two Knauer P120 HPLC pumps for IPA and a 10 vol% nitrobenzene solution in IPA. A series of Bronkhorst mass-flow controllers followed by the pneumatic Swagelok valves to ensure the absence of gas leaks through the mass flow controllers even at the zero setpoint. The pneumatic valves were actuated with compressed air controlled using an Arduino relay module. The gas and liquid streams were combined in a T-mixer and connected to a 1 m tube reactor wall-coated with a 5 wt% Pd/SiO_2 catalyst. The reactor was placed in a convection oven. Downstream from the reactor, a semi-preparatory filter was connected followed by an Equilibar back-pressure regulator controlled with a Proportion air QB1S regulator. The product feed in a 1.60mm OD, 0.5mm ID FEP tube passed through an Optek (OPB350W125Z) liquid sensor and was analysed by an online Shimadzu GC-2010 equipped with an RTX-1 10m x 0.15mm x 0.15 μm column. The GC was not used in this example for the reactor control, but only for validation of the reactor performance.

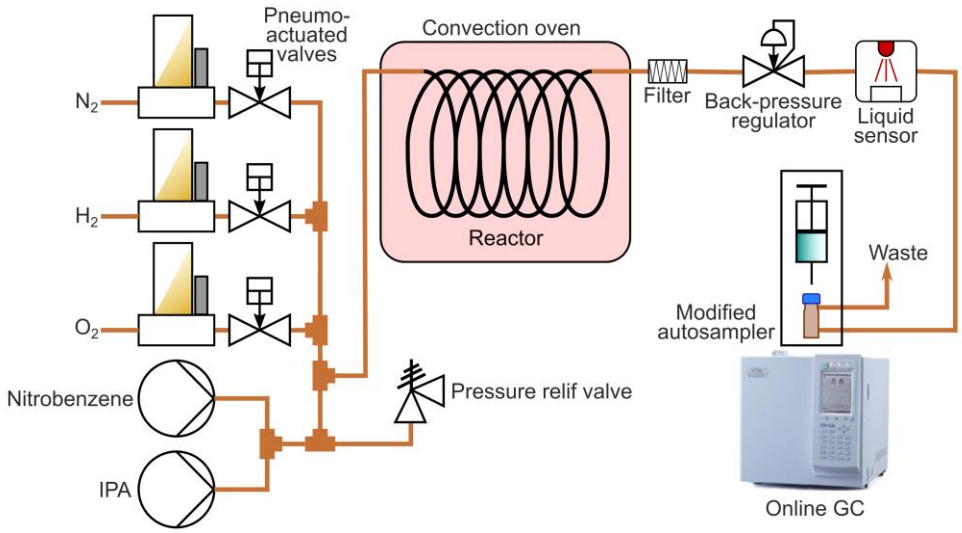

Figure 5. Scheme of the reactor used in the nitrobenzene hydrogenation with the concentration controlled with a PID (proportional–integral–derivative) algorithm.

Figure 6 shows the automation structure used that contains two horizontal systems: the OpenFlowChem flow reactor and the OpenFlowChem control system. The reactor system includes device monitors for the individual reactor components. The relay module for the pneumatic valves and the mass-flow controllers were combined in a pseudo instrument by connecting two corresponding device monitors. The pseudo instrument is treated by the flow reactor as a single device monitor and provides a synchronized operation of the interconnected instruments. In this example, the pneumatic valves corresponding to Bronkhorst mass-flow controllers open if a positive setpoint is requested by a device monitor.

The OpenFlowChem control system contained only one device monitor for the Ardunio microcontroller connected to the liquid sensor. The system module adjusted the flow rate of nitrobenzene at a fixed total liquid flow rate and the hydrogen to substrate ratio of 1.15 to maintain the liquid hold-up in the product feed at 93%. The setpoint of 93% was selected to keep a hydrogen excess that is reliably measurable, but small enough to ensure maximum residence time in the reactor. Considering that the liquid hold-up was measured under ambient pressure (after the back-pressure regulator), under the reaction pressure of 10 bar, the liquid hold-up was 99.3%. Therefore, the reactor at the outlet contained a very small amount of gas resulting in the maximum liquid residence time and the reactor throughput.

Two systems, the reactor and control system, were interacting via a control text file – the control system added a new line with a complete set of experimental parameters every 2 minutes. Once the file was updated, it was read by the flow reactor that sent all the setpoint parameters to the instrument and monitored for safe operation.

This example deliberately shows the system structure that provides modularity and allows for interaction with external software via text files. The text files also provide an excellent activity log and allow for one step internet of things implementation discussed in example 3.3. The system described was plumbed and assembled in about 4 days, while creating the software using the existing device monitors took only about 5 h.

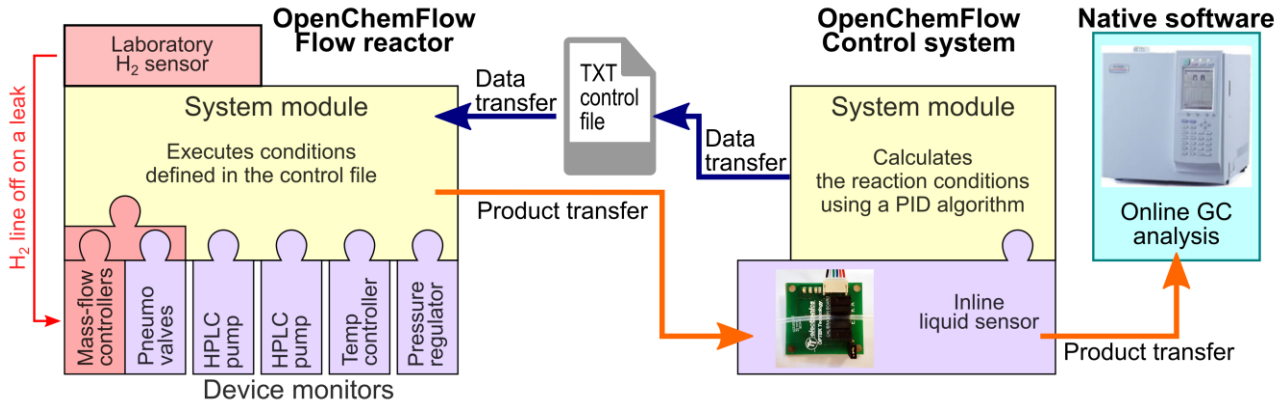

Figure 6. Scheme of the OpenFlowChem automation system with the jigsaw joints showing digital communication. The PID-controlled chemical reactor was built using three components: (i) the OpenFlowChem flow reactor, (ii) the OpenFlowChem control system, and (iii) an online GC with the native software for independent validation of the reactor operation.

Figure 7 shows the scheme of nitrobenzene hydrogenation. The main product observed was aniline, in agreement with the literature on the nitrobenzene hydrogenation over Pd-based catalysts.[62–64] We did not attempt additional product analysis using, for example, NMR for two reasons. Firstly, the main reaction products for the reaction over Pd catalysts are well known. The gas chromatography provided good separation of all the expected products and the substrate. Secondly, the carbon balance was always above 98 % confirming that all the major products are accounted for.

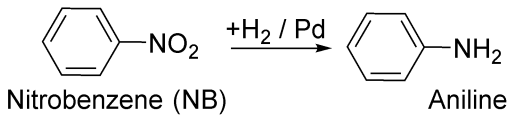

Figure 7. Scheme of nitrobenzene hydrogenation over a Pd/SiO_2 catalyst.

Figure 8 shows the results and the main parameters logged by the PID-controlled reactor. At the initial moment, the reaction temperature was increased to 90 °C, while the nitrobenzene concentration and the proportional hydrogen flow were gradually decreasing because the liquid hold up was below the setpoint. After 1.2 hours on stream and minor oscillations, the liquid fraction reached the setpoint. The oscillatory behaviour observed here is typical for PID controllers and can be improved adjusting the control parameters balancing between the amplitude of oscillations and speed of reaching the steady state.[65–67] After about 1.5 hours on stream, the liquid fraction showed minor fluctuations around the nitrobenzene concentration of 2 vol%. During this period, the product analysis showed full conversion confirming the correctness of operation.

Obviously, this operation could have continued for many days, and the nitrobenzene concentration would have gradually decreased as a result of catalyst deactivation. To demonstrate this behaviour in a shorter time, the reaction temperature after 4 hours on stream was decreased by 10 °C in 0.5 h which resembles catalyst deactivation. In response to this change, the OpenFlowChem system automatically decreased the nitrobenzene flow rate from 182 µL min^{-1} to 162 µL min^{-1} to adjust for the lower reaction

rate. The change in the catalyst activity with the decreasing temperature was gradual to maintain full nitrobenzene conversion.

The second disturbance was introduced at a time on stream of 5.2 h when the temperature was further decreased by 10 °C during 0.5 h, which resulted in a more significant change in the reaction rates. In response, the system reduced the nitrobenzene flow rate to 91 μL min^{-1} and stabilised at a lower concentration to provide full nitrobenzene conversion.

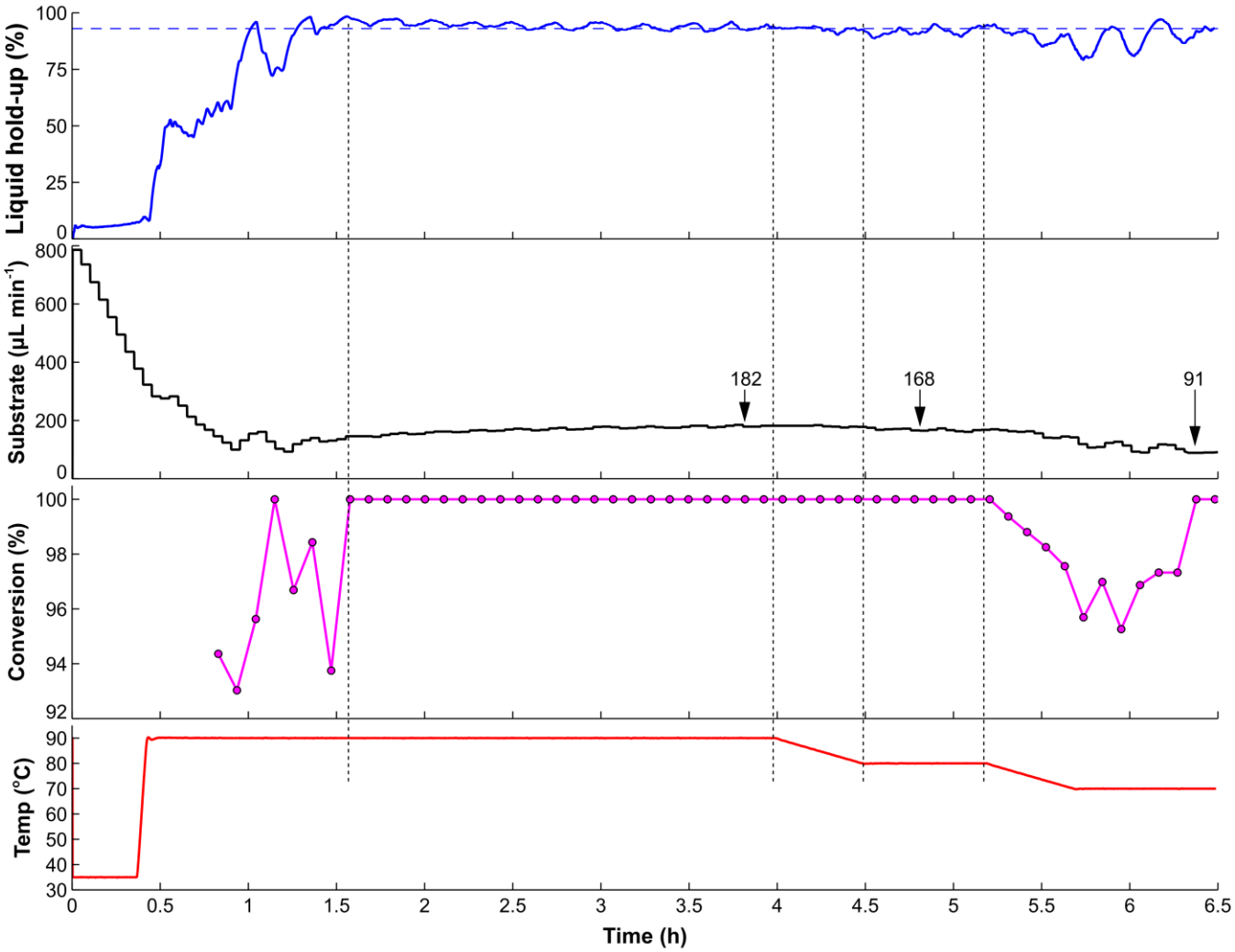

Figure 8. Main parameters of the PID-controlled nitrobenzene hydrogenation reactor that maintained the liquid hold-up of 93 % after the 1 m reactor wall-coated with a 5 wt% Pd/SiO_2 catalyst. The flow rates of nitrobenzene and IPA were adjusted by the OpenFlowChem system at the total flow rate of 1 mL min^{-1} and the H_2 to substrate molar ratio of 1.15 at the reaction pressure is 10 bar(g).

The PID-controlled hydrogenation shows the ability to react on the changing external parameters or catalyst deactivation while keeping the reactor performance at the optimal level and full substrate conversion even despite minor disturbances. Importantly, the system had no information about the system except the theoretical hydrogen to substrate ratio. In this example, the substrate flow was adjusted to ensure full conversion, but it is possible to increase the reaction temperature or pressure as

industrially implemented in many processes. An additional advantage of operating under hydrogen excess is the decrease in the catalyst leaching,[58] which was found experimentally to be only 0.93 parts per billion (ppb).

3.3. Self-optimisation of the catalyst poisoning level

In the last example, the OpenFlowChem performed self-optimisation of the MBY semihydrogenation reaction (Figure 4a). Three independent parameters were optimised: the flow rates of the substrate (MBY), catalyst poison (quinoline) and IPA solvent at a fixed temperature, pressure and the H_2 to the substrate ratio. A full 6-dimensional optimisation with all the parameters could have been performed using the same approach. However, we limited the problem to 3 degrees of freedom to demonstrate a sufficiency challenging yet representative real-life optimisation problem encountered in many flow chemistry applications.

The system similar to that described in section 3.2 was used in the self-optimisation with only an HPLC pump (Knauer P4.1S) added. The liquid feeds were IPA, a 1 M MBY solution in IPA and 2 M quinoline in IPA. The H_2 flow rate maintained the H_2 to substrate molar ratio of 1.2 at the reaction temperature 40 ^oC and 0.2 bar (g) pressure. The reaction was carried out inside a 1 m tube reactor wall-coated with a 5wt% Pd/SiO_2 catalyst. The products were analysed with an online GC was equipped with a Stabilwax 10 m x 0.15 mm x 0.15 μm column, optimised for quick separation of the reaction components and sampling every 2.5 minutes. The sampling was performed using a standard autosampler with a modified flow-through vial with the details shown in the Supplementary S5.

The GC data were processed by the native software (Lab Solutions) and exported as text files with the concentrations of all the components. A possibility to export results as text files exists in many analytical instrumentation systems and provides an opportunity to establish a simple instrument-reactor communication. While Jensen et al.[12,32,34] created a bespoke software to determine the product concentration from the HPLC data, existing commercial software provides quick implementation and many advanced functionalities such as peak detection and baseline correction.

Figure 9 shows the scheme of the self-optimisation system. The gas-liquid product flow from the OpenFlowChem reactor went into the online GC. A text file with the analysis results was created for every analysis and uploaded to a cloud storage (Dropbox). Once uploaded, the file was analysed on a different computer with a standalone MATLAB program that calculated new flow rates of MBY, quinoline and the solvent, which were recorded into the reactor control text file.

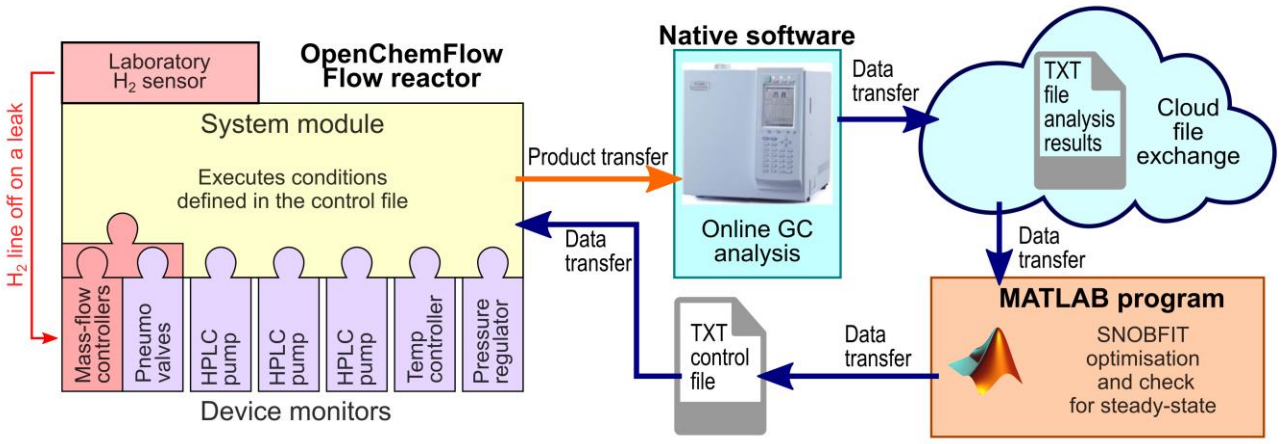

Figure 9. Scheme of the OpenChemFlow self-optimisation reactor containing (i) a flow reactor, (ii) a MATLAB program calculating the next set of experimental conditions and (iii) an online GC with the native software for the analysis of the reaction products with the data transferred to the main computer via the cloud.

Figure 10 shows a block diagram of the MATLAB program that controls the OpenFlowChem reactor. The program (i) obtains the steady-state reactor performance and (ii) optimises the reaction conditions. Steady state data are considered achieved if the product yield changes by less than 3% relative to the previous yield. The optimisation algorithm used in the work is based on the Stable Noisy Optimization by Branch and Fit (SNOBFIT) algorithm developed by Huyer and Neumaier[68] because of its excellent applicability for the real-life systems. The algorithm takes into account the possibility for the experimental noise and avoids false optimisation directions. The algorithm also generates points widely distributed across the chemical space to increase the chances of finding a global rather than a local optimum.

The optimisation algorithm was minimising the objective function shown in Equation 3, where S_{MBE} is the MBE selectivity, X_{MBY} is the MBY conversion and Q_{MBY} is the flow rate of the MBY solution.

$$F_{objective} = 1 - 0.9 \cdot (S_{MBE} \cdot X_{MBY})^2 - 0.1 \cdot \frac{Q_{MBY}}{2000} (\mu L\ min^{-1}). \quad (3)$$

The objective function can be selected arbitrarily as long as it codifies the desired optimisation outcome in mathematical terms of the measurable parameters. In our case, we selected the squared yield to increase the importance of the product yield approaching 100%. The term containing the flow rate demonstrates that the high substrate flow is also desired, but with no compromise for the yield. In this equation, we did not include an explicit contribution of the solvent and quinoline flow rates because they were implicitly involved in S_{MBE} and X_{MBE} via decreasing residence time and poisoning.

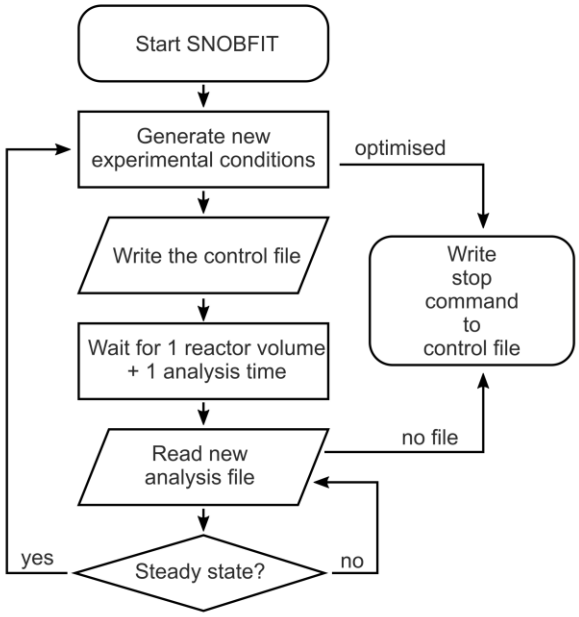

Figure 10. Block diagram of the MATLAB program that controls the self-optimisation OpenFlowChem flow reactor.

Figure 11 shows the results of the self-optimisation study. The wide distribution of points generated by the optimisation algorithm provides sufficient confidence in finding the global minimum of the objective function, which was observed at the substrate flow rate of 100 μL min^{-1}, quinoline flow of 165 μL min^{-1} and the solvent flow of 200 μL min^{-1}. Under these conditions, the MBE yield reached 96.5% at the MBY conversion of 98.6% and the MBE selectivity of 97.9%. Considering that an inferior Pd/SiO_2 catalyst was taken, the result is remarkably high and comparable to bimetallic Pd catalysts (notably Lindlar) and Pd-Zn(ZnO) catalysts,[46,48,49,52,55,69–74] which demonstrates the capability of self-optimising systems.

Self-optimisation of metal-catalysed reactions is significantly different compared to the previously studied acid-catalysed of non-catalytic reactions.[10,26,29,30,33,34,36] In our examples, the attainment of the steady state cannot be guaranteed after 3-5 reactor volumes. Steady state has to be checked experimentally because the equilibration time is affected by the substrate and quinoline concentrations, which in turn depend on the three flow rates. Therefore, the transient reaction analysis methods in studying the reaction kinetics might become limited or generate data not representative to the steady-state operation.[12,18,38]

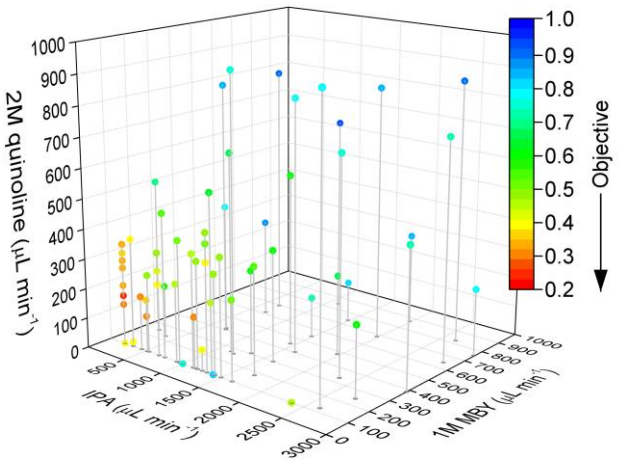

Figure 11. Results of MBY semihydrogenation self-optimisation in a tube reactor wall-coated with 5 wt% Pd/SiO_2. The flow rates of the 1 M MBY solution in IPA, 2 M quinoline in IPA and IPA were optimised at the fixed H_2 to substrate molar ratio of 1.2 at the reaction temperature of 40 °C and the pressure of 0.2 bar (g).

The modification of the OpenFlowChem system module from example 3.2 to 3.3 required less than 1h. The Matlab program development based on the SNOBFIT algorithm took 12 h, which was comparable to 3 h needed to configure the experimental hardware. Such quick automation was achieved using commercial analytical software and introducing only minor changes into the OpenChemFlow system.

The communication protocol between the OpenFlowChem module and the analytical instrumentation system via text files provides an excellent opportunity for the internet of things (IoT) operation using standard Cloud-based file exchange software. This approach provides good data security with only one internet connection point via a well-tested, constantly updated file exchange software. The multi-point approaches (with multiple hardware and software protocols, specific for every device) are difficult to keep updated and show a higher vulnerability as evidenced by the recent ransomware computer attacks.[75–78]

4. Conclusions

We introduced OpenFlowChem, a novel platform for the flow chemistry automation with the minimal efforts and maximum flexibility. Using the platform, new automation systems can be created or modified within hours – the time comparable to connecting and setting up the experiment hardware. The source codes and the device monitors (the most time-consuming part) are freely available on the web[39] making many experiments a matter of plugging the programming modules and pulling the system logic together.

The platform was demonstrated in three examples of the hydrogenation reactions performed inside catalyst-coated tube reactors with the increasing complexity of the automation tasks. The automatic stepwise operation – executing predefined steps allows for efficient routine tests and the experiments that require rather high temporal resolution possible with fraction collectors. As a result, we have shown that the quinoline poisoning of the Pd catalyst is reversible, but the time required to achieve the steady state significantly increases at a high quinoline concentration.

The example of the PID-controlled reaction with the fixed hydrogen consumption shows the possibility to find optimal reaction conditions with only theoretical hydrogen consumption known in advance. The PID operation allows carrying out the reactions with the maximum reactor throughput and adjusts the

reaction conditions to compensate for the catalyst deactivation. To perform this example, we used, likely, the least costly inline sensor – the 10$ optical liquid sensor to measure the hydrogen consumption and found that it has several advantages over the conventional mass-flow meters.

Lastly, we demonstrated the application of the OpenFlowChem platform in the 3-dimensional self-optimisation of an alkynol semihydrogenation reaction. The system used an online GC for the feed analysis and a standalone MATLAB program operating independently on different computers interacting via the internet of things. In the example, the reactor was autonomously operating and adjusted the flow rates of the substrate, catalyst poison and the solvent to minimise the objective function. As a result, an excellent yield of the intermediate alkene product of 96.5% was demonstrated even with a sub-optimal Pd/SiO_2 catalyst.

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